

# Prevention of the Dawn Phenomenon (Early Morning Hyperglycemia) in Insulin-Dependent Diabetes Mellitus by Bedtime Intranasal Administration of a Long-Acting Somatostatin Analog

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Current evidence indicates that resistance to insulin due to nocturnal secretion of growth hormone plays an important role in the Dawn phenomenon and that day-to-day variability in growth hormone secretion makes this condition difficult to manage. We therefore assessed the effect of a long-acting somatostatin analog (L363,586) on overnight plasma glucose and growth hormone levels in six patients with insulin-dependent diabetes mellitus. The analog (600 µg) was administered intranasally at bedtime to determine whether the inconvenience of an additional injection could be avoided. Compared to control experiments, in which saline was administered intranasally, overnight increases in plasma glucose concentrations were reduced in all subjects by nearly 70% ( $48 \pm 19$  v  $148 \pm 26$  mg/dL,  $P < .01$ ), plasma growth hormone was maintained at basal levels throughout the night ( $<2$  v  $8$  to  $12$  ng/mL,  $P < .01$ ), and the analog was well tolerated. We conclude that pharmacologic blockade of growth hormone secretion may be a helpful approach to management of the Dawn phenomenon when it cannot be done safely and effectively by adjusting insulin doses.

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THE DEVELOPMENT of hyperglycemia overnight can be a difficult clinical problem in patients with insulin-dependent diabetes mellitus (IDDM), as well as those with noninsulin-dependent diabetes mellitus (NIDDM).<sup>1,2</sup> When this occurs without antecedent hypoglycemia and cannot be explained simply on the basis of waning of previously injected insulin, it is commonly referred to as the Dawn phenomenon.<sup>2-13</sup> Several recent studies,<sup>6-14</sup> in particular those<sup>11-14</sup> demonstrating that intravenous infusion of somatostatin, an inhibitor of growth hormone secretion,<sup>15</sup> markedly attenuates or prevents this overnight hyperglycemia in IDDM patients, have provided evidence that the exaggerated nocturnal surges in growth hormone secretion found in patients with diabetes mellitus<sup>16,17</sup> play an important role in this phenomenon.

A major problem in management of the Dawn phenomenon is its day-to-day variability,<sup>2,9</sup> which is presumably due to erratic nocturnal growth hormone secretion.<sup>6,8,10</sup> Thus, an increase in insulin dose may be inadequate to prevent early morning hyperglycemia one day but may cause nocturnal hypoglycemia on another day.<sup>18</sup> Consistent suppression of nocturnal surges in growth hormone secretion could alleviate this problem. Although this could be achieved with somatostatin,<sup>19</sup> the short half-life of this peptide<sup>15</sup> would require its being infused, which is not practical. However, longer acting and more potent analogs of somatostatin are now available<sup>20-22</sup> and are being used in the treatment of acromegaly.<sup>23</sup> We therefore undertook the present study to determine whether the Dawn phenomenon could be prevented by one of

these analogs (L363,586),<sup>24</sup> the cyclic hexapeptide, cyclo-[N-Me-Ala-Tyr-D-Trp-Lys-Val-Phe]. For this purpose, we used the development of early morning hyperglycemia during overnight constant intravenous infusion of insulin as a model for the Dawn phenomenon and assessed the effect of bedtime intranasal L363,586 administration.

## MATERIALS AND METHODS

Informed, written consent was obtained from six volunteers (four men and two women) with IDDM (plasma C-peptide response to 1 mg intravenous glucagon less than 0.1 ng/ml),<sup>25</sup> who were 22 to 36 years of age and within 20% of their ideal body weight. All volunteers took part in two experiments performed in random order; each experiment was separated by at least 1 week. In both experiments, subjects were withdrawn from their intermediate-acting insulin at least 30 hours prior to study, and were subsequently managed with multiple subcutaneous injections of regular insulin as previously described.<sup>26</sup> No subcutaneous regular insulin was given within 12 hours of starting the study. At 5 PM subjects were placed at bedrest in the Clinical Research Center, connected to a closed-loop insulin infusion device (Biostator GC, IIS, Life Science Instruments, Miles Laboratory, Elkhart, IN), and given a standard meal (600 kcal, 47% carbohydrate, 32% fat, and 21% protein). An arm vein contralateral to that connected to the insulin infusion device was cannulated for blood sampling. Subjects were rendered euglycemic (90 to 110 mg/dL) within four hours. At 11 PM the volunteers received either saline or 600 µg L363,586 dissolved in saline (20 mg/mL) as a nasal droplet. The Biostator variable insulin infusion was stopped at midnight and the apparatus was programmed (7:1 mode) to deliver insulin at the constant rate of 0.15 mU/kg/min, an infusion rate determined from our previous studies to be sufficient to maintain euglycemia between midnight and 3 or 4 AM.<sup>26</sup> Blood was drawn every 30 minutes for measurement of plasma L363,586,<sup>26</sup> free insulin,<sup>24</sup> growth hormone,<sup>27</sup> glucagon,<sup>28</sup> cortisol,<sup>29</sup> and glucose concentrations (YSI glucose analyzer, Yellow Springs, OH) from midnight until completion of the study at 7 AM. All subjects were able to sleep between 11 PM and 7 AM.

Data were given as mean  $\pm$  SEM. Statistical analyses were performed using paired Student *t*-tests.

## RESULTS

### Plasma L363,586 Concentrations

Peak plasma L363,586 concentrations ( $1.68 \pm 0.05$  ng/mL) were observed within one hour after administration at

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## DAWN PHENOMENON AND SOMATOSTATIN

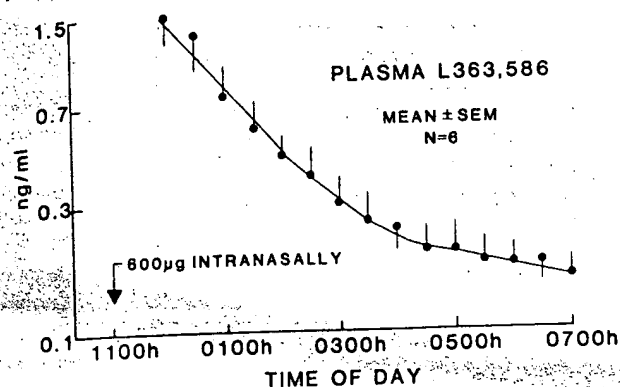


Fig 1. Plasma L363,586 levels after intranasal administration.

midnight, the earliest sampling time (Fig 1). Subsequently, values decreased in a biexponential manner and were still detectable at 7 AM ( $0.17 \pm 0.04$  ng/mL). The initial plasma levels had an apparent half-life of approximately one hour, whereas values beyond four hours after administration had an apparent half-life of about four to five hours.

#### Plasma Glucose Concentrations

Baseline plasma glucose concentrations at midnight were similar after administration of saline ( $98 \pm 5$  mg/dL;  $5.5 \pm 0.5$  mmol/L) (Fig 2). In control (saline) experiments, plasma glucose increased progressively after 2 AM by nearly 150 mg/dL ( $8.3$  mmol/L) to  $247 \pm 29$  mg/dL;  $13.7 \pm 1.6$  mmol/L at 7 AM,  $P < .01$ . After L363,586 administration, plasma glucose did not increase significantly until after 6 AM and then increased only one third as much as in control experiments ( $P < .01$ ) to  $145 \pm 23$  mg/dL ( $8.1 \pm 1.2$  mmol/L).

#### Plasma Growth Hormone, Glucagon, Cortisol, and Free Insulin Concentrations

In control experiments, plasma growth hormone concentrations increased intermittently in individual subjects between midnight and at 3 AM with values averaging  $9.1 \pm$

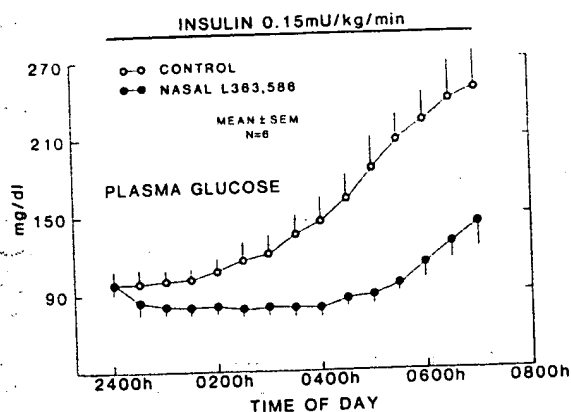


Fig 2. Overnight plasma glucose concentrations of IDDM subjects after intranasal administration of saline or the long-acting somatostatin analog L363,586.

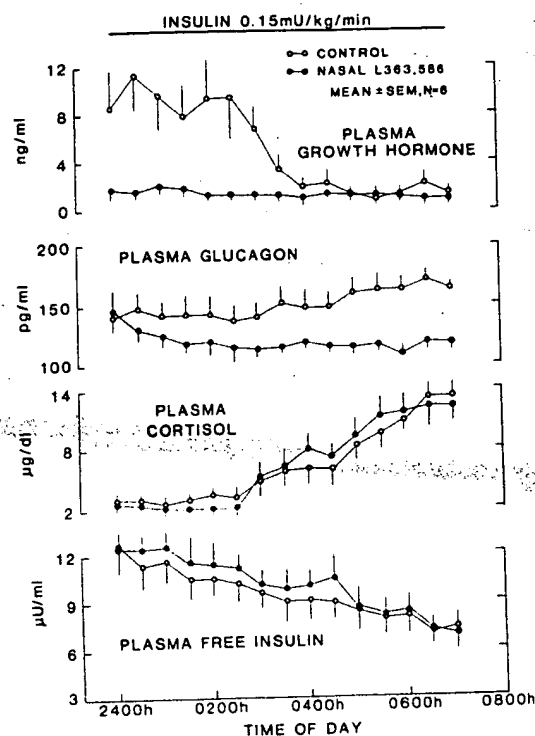


Fig 3. Overnight plasma growth hormone, glucagon, cortisol, and free insulin concentrations of IDDM subjects after intranasal administration of saline or the long-acting somatostatin analog L363,586.

1.6 ng/mL during this period (Fig 3). After L363,586 administration plasma growth hormone remained at basal values during this period ( $1.6 \pm 0.1$  ng/mg,  $P < .01$ ) and throughout the entire night. Plasma glucagon concentrations at midnight were not significantly different on the two study days; in control experiments, plasma glucagon remained relatively constant from midnight to 7 AM ( $139 \pm 10$  v  $164 \pm 5$  pg/mL, respectively, NS). After L363,586 administration, plasma glucagon decreased significantly from  $146 \pm 22$  pg/mL at midnight to  $118 \pm 9$  pg/mL at 7 AM,  $P < .01$ , with mean values during this period being about 20% lower than those observed in control experiments. Plasma cortisol concentrations increased progressively after 2 AM on both study nights, with no significant difference between the two experiments. Plasma free insulin concentrations decreased overnight to a comparable extent in control (from  $12.8 \pm 2.1$  to  $7.6 \pm 1.8$   $\mu$ U/mL,  $P < .05$ ) and L363,586 experiments (from  $12.7 \pm 2.4$  to  $7.3 \pm 1.8$   $\mu$ U/mL,  $P < .05$ ).

#### DISCUSSION

The recent evidence (6-14) for an important role for growth hormone in the pathogenesis of the Dawn phenomenon explains several features of this condition and provides the rationale for attempts at pharmacologic intervention. Although nocturnal surges of growth hormone secretion occur in nondiabetic individuals,<sup>30</sup> they are greater in patients with diabetes mellitus.<sup>16,17</sup> This, together with the inability of diabetic patients to compensate with an appropri-

ate increase in insulin secretion, probably explains why early morning hyperglycemia occurs in diabetic patients but not nondiabetic individuals.<sup>30,31</sup> Improvement of diabetic control, which diminishes growth hormone secretion,<sup>16,17</sup> could account for attenuation of the Dawn phenomenon seen in some patients on intensive insulin therapy.<sup>18</sup> Finally, day-to-day variability of nocturnal growth hormone secretion could explain the unpredictability of the Dawn phenomenon,<sup>2,9</sup> which makes its treatment with increased doses of insulin not only difficult but also potentially hazardous due to the risk of nocturnal hypoglycemia.<sup>18</sup>

Nevertheless, the demonstration of an important role for growth hormone in the Dawn phenomenon<sup>6,14</sup> suggests that pharmacologic blockade of nocturnal growth hormone secretion might be a safer and more effective therapeutic approach to this condition, since it could alleviate its day-to-day variability and result in more consistent insulin requirements. Therefore, in the present studies, we assessed whether pre-bedtime administration of a long-acting somatostatin analog, L363,586, could effectively suppress the Dawn phenomenon in IDDM patients. The analog was administered intranasally to determine whether the inconvenience of an additional subcutaneous injection could be avoided.

We found that the analog administered in this way completely suppressed surges in growth hormone secretion throughout the night and lowered plasma glucagon levels without affecting changes in plasma cortisol and free insulin concentrations. Since there was no evidence for a rebound increase in either plasma glucagon or growth hormone levels, such as is observed after termination of intravenous infusion of short-acting somatostatin,<sup>32</sup> it is likely that the plasma L363,586 concentration eight hours after administration ( $0.17 \pm 0.4$  ng/mL) was still active in suppressing the secretion of these hormones.

The pre-bedtime intranasal administration of the long-acting somatostatin analog reduced the approximate 150 mg/dL increase in plasma glucose concentration observed in control experiments to less than 50 mg/dL. Presumably, if plasma free insulin concentrations had not decreased overnight due to the waning of Biostator insulin delivery, which has been documented in several recent studies,<sup>7,33,34</sup> there would have been even less early morning hyperglycemia. Nevertheless, we cannot exclude the possibility that mere reduction of insulin requirements in some patients during this relative hypoinsulinemia was the main mechanism by which the somatostatin analog reduced fasting hyperglycemia. It deserves emphasis, however, that this reduction in early morning hyperglycemia occurred in the face of there being identical plasma free insulin concentrations in control and L363,586 studies.

Although the Dawn phenomenon has been shown to occur under conditions in which plasma glucagon concentrations have been maintained constant,<sup>11,12,14</sup> one cannot exclude the possibility that inhibition of glucagon secretion contributed to the lower plasma glucose concentrations after administration of L363,586. However, it is doubtful that this played the predominant role for several reasons. First of all, the onset of inhibition of glucagon secretion by the analog was rapid. If

this suppression of glucagon secretion exerted a major influence on plasma glucose levels, one would have expected a decrease in plasma glucose to be evident within one to two hours, not three to six hours later.<sup>15</sup> Moreover, the main effect of the analog was to prevent an increase in plasma glucose, but in the control experiments there was no increase in plasma glucagon. The main effect of the analog was to prevent a late increase in plasma glucose occurring three to four hours after a period of increased growth hormone secretion. This effect is consistent with its acting primarily through suppression of growth hormone secretion because the insulin antagonistic effects of growth hormone usually require several hours to become evident.<sup>35</sup>

Nonetheless, the fact that glucagon is an important counter-regulatory hormone<sup>36</sup> raises the question whether overnight inhibition of glucagon and growth hormone secretion may predispose patients to the risk of nocturnal hypoglycemia. However, the glucagon response to hypoglycemia is absent or markedly diminished in most patients with IDDM,<sup>37</sup> and growth hormone is not presently considered to be an important immediate defense against hypoglycemia.<sup>36</sup> Furthermore, epinephrine, whose secretion is not affected by somatostatin and its analogs,<sup>15</sup> can compensate for deficient glucagon secretion and is the major counter-regulatory hormone in diabetic patients with impaired glucagon secretion.<sup>36</sup> Thus, if insulin doses are properly titrated, inhibition of glucagon and growth hormone secretion by L363,586 should not present an additional major risk for nocturnal hypoglycemia.

Finally, L363,586 was well tolerated by all the participants in the study with only one patient complaining of transient mild abdominal discomfort. Administration of somatostatin<sup>15</sup> or its analogs<sup>22,25</sup> in close proximity to taking meals can cause severe abdominal discomfort and diarrhea. Administration of L363,586 at bedtime apparently avoids these problems. However, such use would be contraindicated in children and adolescents because it probably would impair growth.

In summary, the present studies indicate that pre-bedtime intranasal administration of a long-acting somatostatin analog markedly attenuates the Dawn phenomenon in patients with IDDM and is well tolerated. Although additional studies are necessary to assess the long-term safety and efficacy of this agent, our results suggest the pharmacologic blockade of nocturnal surges in growth hormone secretion may represent a helpful approach to management of the Dawn phenomenon when this cannot be done safely and effectively by mere adjustment of insulin doses.

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